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22JUL03 E824374-1 D02890
P01/7700 0.00-0317092.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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NP9 1RH

1. Your reference	REP07543GB	
2. Patent application number *(The Patent Office will fill in this part)*	0317092.5	21 JUL 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Cambridge University Technical Services Ltd. The Old Schools Trinity Lane Cambridge CB2 1TS	
Patents ADP number *(if you know it)*	8206484001	
If the applicant is a corporate body, give the country/state of its incorporation	UK	
4. Title of the invention	Holographic Sensor	
5. Name of your agent *(if you have one)*	Gill Jennings & Every	
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Broadgate House 7 Eldon Street London EC2M 7LH	
Patents ADP number *(if you know it)*	745002	

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* — YES

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	~~4~~
Claim(s)	1
Abstract	
Drawing(s)	4 + 4

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature: Gill Jennings & Every

Date: 21 July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry
020 7377 1377

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Notes

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c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

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HOLOGRAPHIC SENSOR

Field of the Invention

This invention relates to a sensor that is especially suitable for use in the form of a subcutaneous implant.

Background to the Invention

WO-A-9526499 discloses a holographic sensor, based on a volume hologram. This sensor comprises an analyte-sensitive matrix having an optical transducing structure disposed throughout its volume. Because of this physical arrangement of the transducer, the optical signal generated by the sensor is very sensitive to volume changes or structural rearrangements taking place in the analyte-sensitive matrix as a result of interaction or reaction with the analyte.

An alternative method of production for a holographic sensor is disclosed in WO-A-9963408. A sequential treatment technique is used, wherein the polymer film is made first and sensitive silver halide particles are added subsequently. These particles are introduced by diffusing soluble salts into the polymer matrix where they react to form an insoluble light-sensitive precipitate. The holographic image is then recorded.

Such a holographic sensor is made by recording a hologram as a plain mirror which is holographed in a trough of suitable liquid. This arrangement may not always be effective if the sensor is used in an environment where there is considerable light scatter, e.g. subcutaneously.

Summary of the Invention

The present invention is based on a realisation of the value of changing the known arrangement to a hologram of a concave mirror. This allows a wide range of possible uses, e.g. as a small subcutaneous implant which can be conveniently interrogated using a fibre optic bundle. Furthermore, to overcome the major obstacle of the problem of light scatter, the replay wavelength range can be adjusted to extend well into the near infra-red (NIR).

Description of Preferred Embodiments

A holographic sensor of the type used in this invention generally comprises a holographic support medium and, disposed throughout the volume of the medium, a hologram. The support medium interacts with an analyte

resulting in a variation of a physical property of the medium. This variation induces a change in an optical characteristic of the holographic element, such as its polarisability, reflectance, refractance or absorbance. If any change occurs whilst the hologram is being replayed by incident broad band, non-ionising electromagnetic radiation, then a colour or intensity change, for example, may be observed.

There are a number of basic ways to change a physical property, and thus vary an optical characteristic. The physical property that varies is preferably the size of the holographic element. This may be achieved by incorporating specific groups into the support matrix, wherein these groups undergo a conformational change upon interaction with the analyte, and cause an expansion or contraction of the support medium. A group is preferably the specific binding conjugate of an analyte species. Another method would be to change the active water content of the support medium.

A holographic sensor may be used for detection of a variety of analytes, simply by modifying the composition of the support medium. The medium preferably comprises a polymer matrix, the composition of which must be optimised to obtain a high quality film, i.e. a film having a uniform matrix in which holographic fringes can be formed. The matrix is preferably formed from the copolymerisation of (meth)acrylamide and/or (meth)acrylate-derived monomers, and may be cross-linked. In particular, the monomer HEMA (hydroxyethyl methacrylate) is readily polymerisable and cross-linkable. PolyHEMA is a versatile support material since it is swellable, hydrophilic and widely biocompatible.

Other examples of holographic support media are gelatin, K-carageenan, agar, agarose, polyvinyl alcohol (PVA), sol-gels (as broadly classified), hydro-gels (as broadly classified), and acrylates. Further materials are polysaccharides, proteins and proteinaceous materials, oligonucleotides, RNA, DNA, cellulose, cellulose acetate, siloxanes, polyamides, polyimides and polyacrylamides. Gelatin is a standard matrix material for supporting photosensitive species, such as silver halide grains. Gelatin can also be photo-cross-linked by chromium III ions, between carboxyl groups on gel strands.

The sensor may be prepared in the same way as has already been described in the PCT (WO) publications given in the "Background". A suitable arrangement for this purpose is shown in Figure 1 of the accompanying drawings. An alternative method is by silverless double polymerisation, as described in British Patent Application No. 0305590.2.

In the latter case, there would be normally no liquid in the exposure bath in Fig.1. The contents of all these specifications is incorporated herein by reference.

Figure 1 shows a curved concave mirror. The term "concave" is used herein in a broad sense, to describe any arrangement that has a focussing effect. The mirror may be, for example, parabolic or it may comprise flat central and edge portions at an angle to each other.

As indicated above, a sensor of the invention is particularly suitable for use in conjunction with a unit, e.g. of optical fibres, whereby light can be transmitted to and from the hologram. For example, a suitable bundle of fibres, ending in a probe tip, is shown in Fig 2. In a particular embodiment, the probe is about 5 mm in diameter, with an internal ring of 6 fibres, defining a circle 1 mm across, surrounding a central fibre.

In the particular embodiment shown in Fig. 2, the central fibre leads to a spectrometer read-out (not shown) and the ring fibres are connected to a white light illumination source (not shown). Because the tungsten filament of the source does not constitute a perfect point source this arrangement works more efficiently than the alternative of having the central fibre deliver the white light and the ring fibres beaming light back to the spectrometer. An alternative arrangement comprises the "ring" fibres at the spectrometer end in a line one above the other to coincide with the normal spectrometer slit.

The utility of the invention will now be described, with particular reference to Figures 3 and 4.

In Fig. 4, the hologram is shown interrogated in a non-scattering clear environment. The hologram here returns the light as if it were returning from the concave mirror used in Fig 1 to make it. However, because it was made with a particular laser wavelength, it becomes in effect a monochromatic concave mirror

and furthermore since it was made in smart polymer the replay colour will change with its environment. An alternative would be to make it with more than one well separated laser wavelength, enabling it to sense different factors in its environment. For example, it could appear to be simultaneously acting as a green, red or blue concave mirror, with the separation between the wavelengths much greater than the wavelength shifts likely to occur as it acts as a sensor, giving say a range of greens or reds but never large enough to cause ambiguous results from wavelength overlaps. The ability of the sensor to give a well separated response to more than one analyte may be achieved using a sensor having a layered structure, each layer comprising a different material. Alternatively, the sensor may consist of different materials lying concentrically adjacent to each other throughout their depth.

The holographic concave mirror image (which may be aspheric, for example parabolic) focuses the coloured light onto the central fibre. A valuable feature of working on axis (unlike previous work with plane mirrors where the diffracted light was arranged to reflect off at a slightly different angle to the specularly reflected light) is now that as the diffracted wavelength changes it remains focused on the central position.

Fig. 3 shows the same arrangement, but in a diffusing environment. This is typical of a subcutaneous implant.

In use, the intention is not necessarily to track changes in intensity of the returning light. If as much as 99% of the light is lost due to scatter, then being able to track a small wavelength shift in the remaining 1% from a very highly diffracting implanted smart hologram may be satisfactory. In order to reduce the problem of scattered light, it may sometimes be helpful to make the hologram with an off-axis concave mirror.

For use as an implant, the sensor may have to be covered with material to lessen rejection problems. This should not affect say glucose detection or ion detection.

CLAIMS

1. A sensor for the detection of an analyte, which comprises a holographic element comprising a medium and a hologram disposed throughout the volume of the medium, wherein an optical characteristic of the hologram changes as a result of a variation of a physical property occurring throughout the volume of the medium, and wherein the hologram is formed as a concave mirror.

2. A sensor according to claim 1, wherein the physical property is the size of the medium.

3. A sensor according to claim 1 or claim 2, wherein the optical characteristic is the reflectance, refractance or absorbance of the holographic element.

4. A sensor according to any preceding claim, wherein the analyte is present in blood.

5. A sensor according to any preceding claim, wherein the analyte is glucose.

6. A sensor according to any preceding claim, in the form of a subcutaneous implant.

7. A sensor according to any preceding claim, which additionally comprises a unit, e.g. comprising optical fibres, whereby light can be transmitted to and from the hologram.

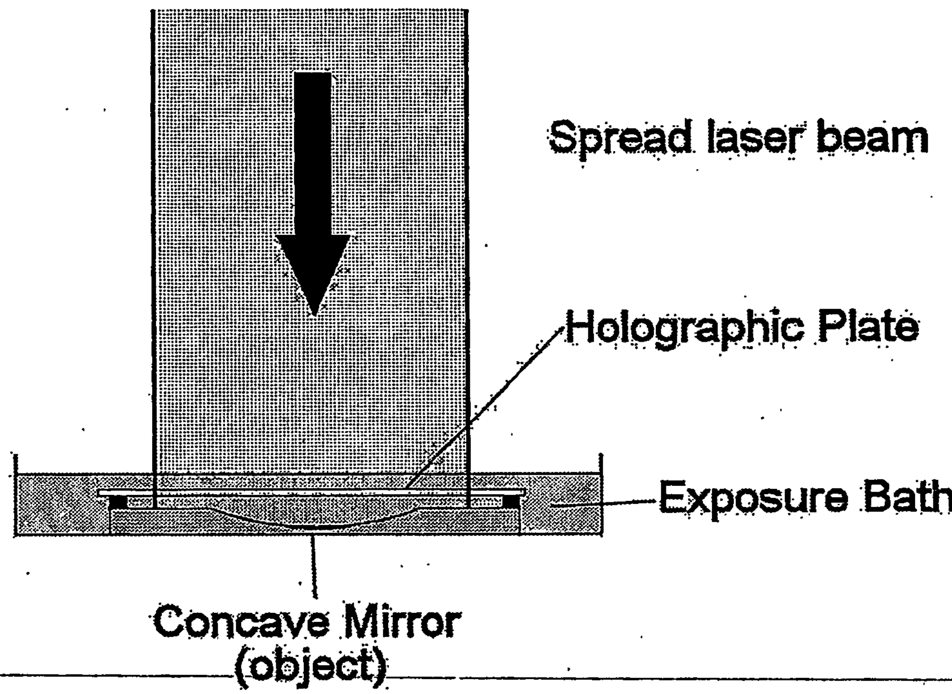
Spread laser beam
Holographic Plate
Exposure Bath
Concave Mirror
(object)

Figure 1

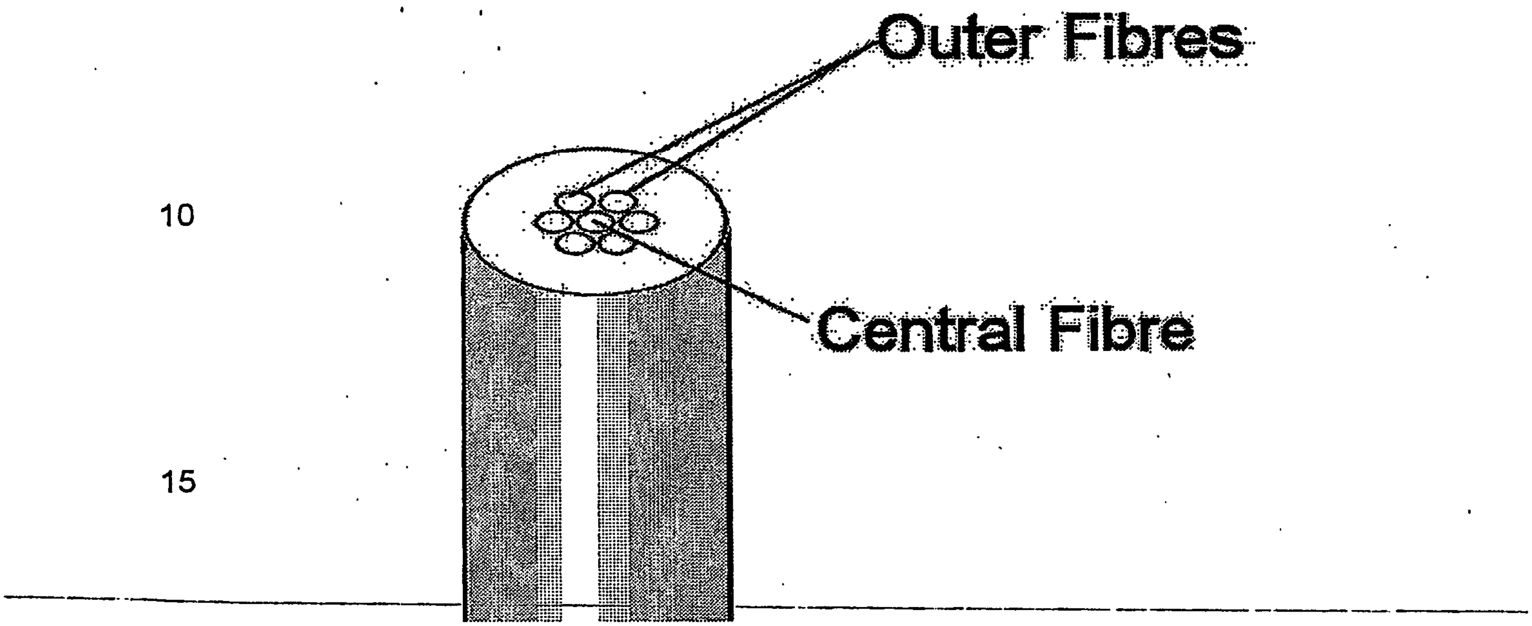

Figure 2

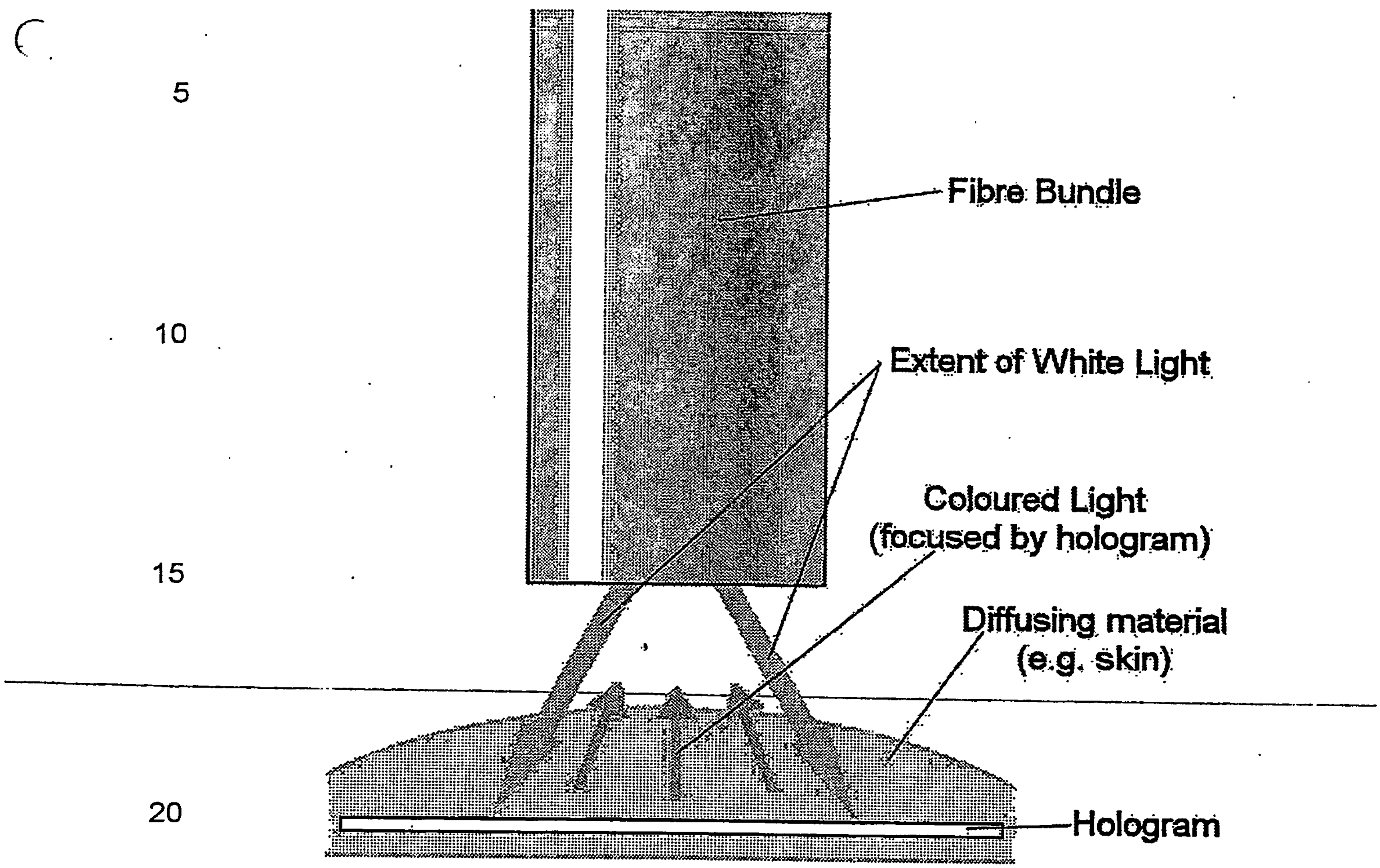
Fibre Bundle
Extent of White Light
Coloured Light
(focused by hologram)
Diffusing material
(e.g. skin)
Hologram

Figure 3

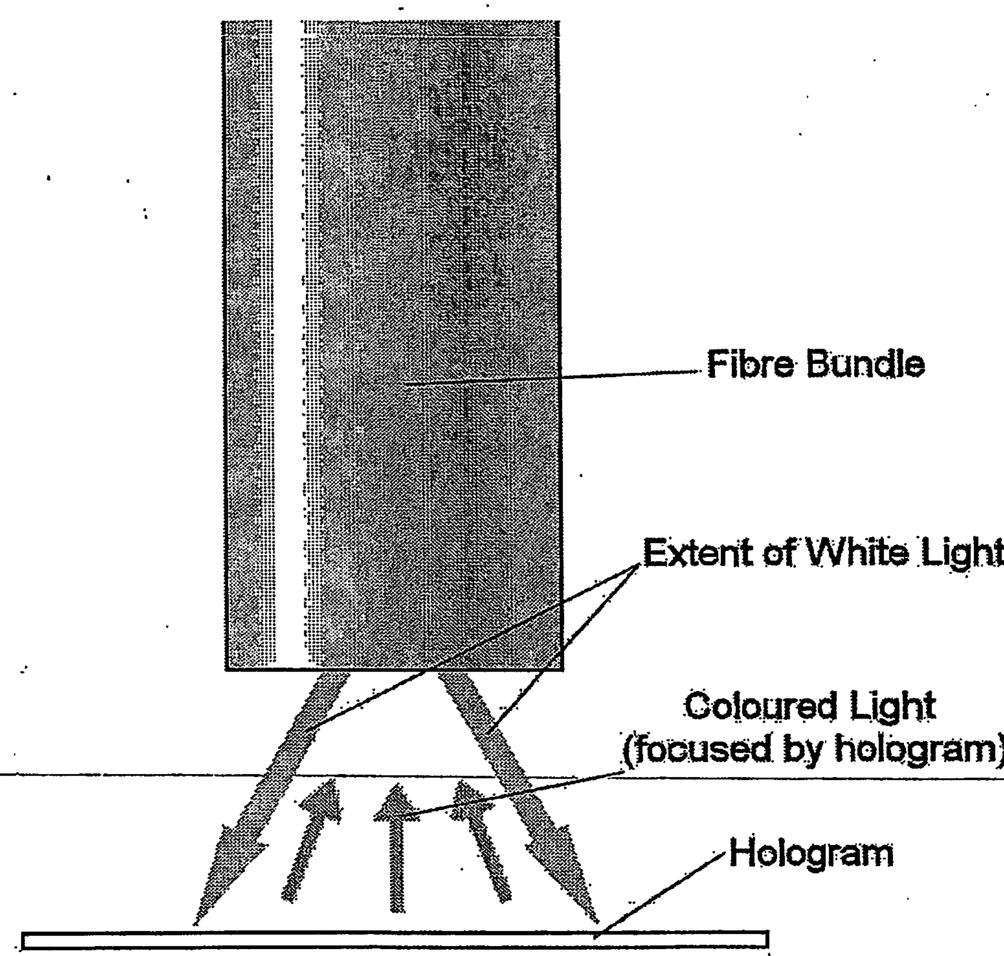
Fibre Bundle
Extent of White Light
Coloured Light
(focused by hologram)
Hologram

Figure 4